Is Progressive Multiple Sclerosis a Gray Matter Disease?

Over the past few years, it has become painfully clear that there is much more to the multiple sclerosis (MS) brain than meets the eye on conventional magnetic resonance (MR) images. Apart from the typical focal lesions in the periventricular white matter (WM), substantial abnormalities can also be found in cortical and subcortical gray matter (GM), and in the "normal-appearing" WM (NAWM).[1,2] Histopathological studies have shown that cortical demyelination may be extensive in chronic MS cases, and in some cases, a pattern of general cortical demyelination may develop, which means that nearly all cortical gyri are affected.[3] Demyelinated cortical lesions may be mixed, that is, they involve both (lower layers of) the cortex and areas of subcortical WM (so-called type I lesions), but more often they are purely intracortical (lesion types II, III, and IV).[1] In a recent postmortem study, it was shown that in the progressive phase of the disease, type III subpial cortical demyelination becomes more prominent and cooccurs with a pattern of diffuse microglial reactivity throughout the WM.[2] Clinically, GM demyelination is of relevance, because it was found that the WM abnormalities visible on MRI cannot explain the full extent of clinical, including cognitive, deficits in MS patients.[4]

It is difficult to detect cortical GM lesions on conventional T2-weighted or even on more advanced fluid-attenuated inversion recovery images because these lesions are largely noninflammatory and generate only little contrast on MRI.[5] However, recent studies have shown that an improvement in cortical lesion detection in MS can be achieved by using a double inversion recovery[6,7] or T1-weighted, three-dimensional, spoiled gradient recalled echo sequence.[8,9] Apart from visualizing cortical lesions, GM damage can be assessed by using quantitative magnetic resonance imaging (MRI) techniques[10–12] or atrophy and cortical thickness measurements,[13,14] which generally correlate well with disability.[10,15] Cortical thickness studies have shown focal thinning of frontotemporal, parietal, precentral, and anterior cingulate cortex,[14,16] largely consistent with histopathological data on the preferential distribution of cortical demyelination in MS.[3] Brain atrophy was reported to be already present in patients with a clinically isolated syndrome (CIS),[17] and to further accrue with disease progression.[18,19] These results notwithstanding, several issues regarding the (separate) evolution of WM and GM atrophy among different MS disease types and stages, the relation between GM and WM atrophy, and their respective effects on disability are still largely unclear.

In this issue of the *Annals of Neurology,* two interesting articles deal with these issues.[20,21] In Fisniku and colleagues'[20] study, a cohort of MS patients with a uniquely long follow-up duration was evaluated to assess tissue-specific atrophy. The patients from this cohort initially presented with a clinically isolated syndrome (CIS) and were subsequently followed for 20 years, undergoing clinical and MRI evaluations at approximately 5-year intervals. The investigators found that the extent of GM atrophy in the MS patients was greater than that of WM atrophy after 20 years of disease, and that there was significantly more GM atrophy, but not WM atrophy, in secondary progressive MS (SPMS) versus relapsing remitting MS (RRMS) patients, as well as in RRMS versus CIS patients who had not had a second episode. The clinical relevance of these findings is illustrated by significant correlations between GM, but not WM, atrophy and disability as measured by Expanded Disability Status Scale and Multiple Sclerosis Functional Composite. GM atrophy proved to be a stronger predictor of disability than focal WM lesion load and WM atrophy. These findings emphasize the need for a better understanding of (increasing) GM damage in MS, as well as the potential usefulness of GM atrophy measurements in natural history studies and treatment trials.

Fisniku and colleagues'[20] study demonstrates that, relative to the WM, GM atrophy is more abundant and more clinically significant in progressive compared with relapsing disease. However, because of its cross-sectional design, this study could not provide any information on the *rate* of GM atrophy. Relatively little is known about GM atrophy rates in MS, although several studies have investigated rates of whole-brain atrophy,[15,22,23] which appears to predict future clinical status.[15,24] In Fisher and coworkers'[21] study, also featured in this issue of the *Annals,* GM atrophy was studied longitudinally in a large group of MS patients who were followed over 4 years, and the authors distinguish between GM and WM atrophy rates across the main MS disease types. They found that, although WM atrophy rate remained constant at threefold normal across all disease stages in their dataset, GM atrophy rate accelerated in the SP phase. Compared with control subjects, a 3.4-fold increase of GM atrophy rate was seen in CIS patients converting to RRMS, whereas a 14-fold increase was measured in SPMS patients. These results, showing that the character of the pathological process changes with advancing disease, with a dominance of GM pathology in the progressive phase, complement Fisniku and colleagues'[20] findings. Interestingly, Fisher and coworkers[21] showed that WM

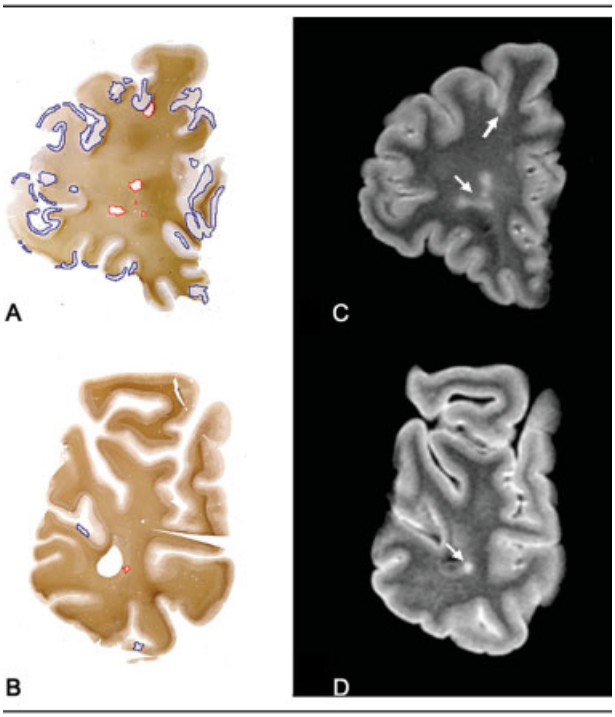

Fig. Paraffin sections immunohistochemically stained with anti-proteolipid protein antibody (A, C) and corresponding T2-weighted magnetic resonance (MR) images from a patient with chronic extensive cortical subpial demyelination (A, B) and from a patient with little cortical demyelination (C, D). Demyelinated cortical areas are visible in immunohistochemical stainings (A, C; blue outlines*) but not on MR imaging (B, D). White matter demyelination (A, C;* red outlines*), detectable by MR imaging (B, D;* arrows*), did not correlate with the extent of cortical gray matter demyelination. (Reprinted from Bo and colleagues,[25] by permission.)*

lesion volume change, WM lesion magnetization transfer ratio, and magnetization transfer ratio of the normal-appearing brain tissue together accounted for a large proportion of the variance in whole-brain and WM atrophy in RRMS and SPMS. In RRMS, these same parameters explained part of the GM atrophy as well. However, no WM correlates were observed for GM atrophy in SPMS patients. All this appears to indicate that GM and WM disease processes are largely unrelated in progressive MS, which confirms histopathology findings where extensive cortical demyelination was found to be unrelated to WM lesion load (Fig).[25]

Fisher and coworkers[21] hypothesize that lesions intrinsic to the GM, not visible on their standard MR sequences, are the major contributors to GM atrophy in progressive MS, and suggest that more advanced MRI techniques be applied in future studies to investigate the relation between GM lesions and GM atrophy. Although such a relation may likely exist, and this issue certainly warrants further investigation, there have also been reports of pathology *outside* of focal GM lesions.[26,27] For example, in a recent histopathology study, Wegner and coauthors[27] describe a 10% overall cortical thickness reduction in their MS cases, which was, at least partly, independent of cortical demyelination. Substantial atrophy with neuronal loss and neuronal shape changes were also found in the MS hippocampus,[28] a nonneocortical structure that is frequently and extensively demyelinated in MS.[29] These changes were more prominent within hippocampal lesions but were also present in nondemyelinated areas. A marked reduction of synapses, suggestive of deafferentation, was found in both demyelinated and normally myelinated MS hippocampus. Furthermore, on a more methodological note, the diffuse and subtle WM inflammation that accompanies increasing GM demyelination in the progressive phase[2] may remain largely undetected by measures such as magnetization transfer ratio.[30] It should be further investigated whether other, perhaps more sensitive, quantitative MR techniques such as T1-relaxometry or diffusion tensor imaging are better capable of detecting these abnormalities in the WM, and whether they are related to the disproportionate increase of GM atrophy in progressive MS.

With these results in hands, it is now important to explore the relative contributions of GM demyelination, neuronal shrinkage/loss, and deafferentation to overall GM atrophy and cortical thinning in MS. Also, the effect of subtle, diffuse WM abnormalities on GM atrophy remain to be addressed in future studies. Meanwhile, Fisniku and colleagues'[20] and Fisher and coworkers'[21] studies have importantly advanced GM research in MS. By using MRI to show that GM atrophy accumulates and even accelerates with disease progression, independently of WM disease, and that GM atrophy is more strongly predictive of clinical disability than WM abnormalities, the investigators have finalized a conclusion that was already hinted at but could not be definitively proved by histopathology.

I always assumed that histology is the gold standard; this is the world turned upside down.

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Neonatal Encephalitis and White Matter Injury: More Than Just Inflammation?

In this issue of *Annals,* Verboon-Maciolek and coworkers[1] show that human parechovirus (HPeV), specifically HPeV3, is an important cause of neonatal viral encephalitis. The six serotypes of HPeVs that are included in the genus *Parechovirus* are small, single-stranded RNA (ssRNA) viruses belonging to the family Picornaviridae.[2,3] These viruses bear many similarities with another and better known Picornaviridae genus, *Enterovirus (EV)*. Indeed, the genus *Parechovirus* began with the reclassification of echoviruses 21 and 22 as HPeV1 and HPeV2 because of molecular and genetic differences from the remainder of EV. These differences are important because they explain, in part, why the usual polymerase chain reaction testing for EV does not detect HPeV. Thus, encephalitic infection by HPeV3 has been overlooked in the past, which is one important point of Verboon-Maciolek and coworkers'[1] article. (Neonatal encephalitis by other HPeV subtypes is extremely rare and is not discussed further.) The encephalitis caused by HPeV3 infection, as well as by EV, is associated with neonatal seizures and with apparent cerebral white matter injury.[1,4] Verboon-Maciolek and coworkers'[1] report has important implications concerning the cause of neonatal viral encephalitis, the differential diagnosis of neonatal seizures, and the pathology and pathophysiology of the white matter injury.

